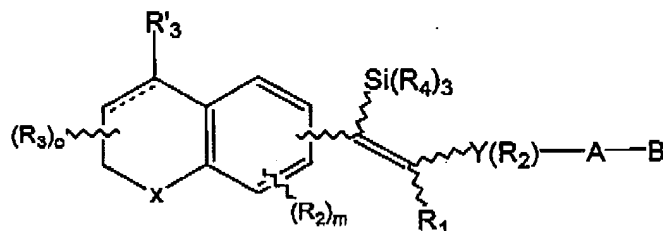


Serial No. : 09/590,447
 Filed : June 9, 2000

AMENDMENTS AND STATUS OF CLAIMS

1. (Currently amended) A method of treating an FXR-mediated pathological condition in a mammal comprising the step of administering to a mammal in need thereof a pharmaceutically acceptable composition comprising a synthetic FXR ligand able to stimulate, block, or inhibit the activity of a mammalian FXR receptor, said synthetic FXR ligand comprising a compound of the formula



formula (3)

wherein the dashed line represents a bond or absence of a bond;

X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons, or

X is $(C(R_1)_2)_n$ where R_1 is H or alkyl of 1 to 6 carbons, and n is an integer having the value of 0 or 1;

R_2 is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 , fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 12 carbons, or alkylthio of 1 to 12 carbons, benzyloxy or $C_1 - C_{12}$ alkylbenzyloxy;

R_3 is hydrogen, lower alkyl of 1 to 6 carbons or F;

m is an integer having the value of 0 - 3;

o is an integer having the value of 0 - 4 when the dashed line represents absence of a bond, and 0 - 3 when the dashed line represents a bond;

$[R_3]$ R'_3 is hydrogen, lower alkyl of 1 to 6 carbons, F or $(R_{15})_r$ -phenyl, $(R_{15})_r$ -naphthyl, or $(R_{15})_r$ -heteroaryl where the heteroaryl group has 1 to 3 heteroatoms selected from the group consisting of O, S and N, r is an integer having the values of 0 - 5;

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R_4 is alkyl of 1 to 8 carbons, or phenyl;

Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups;

R_{15} is independently H, F, Cl, Br, I, NO_2 , $N(R_8)_2$, $NH(R_8)$, COR_8 , $NR_8CON(R_8)_2$, OH, $OCOR_8$, OR_8 , CN, an alkyl group having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10 carbons, an alkenyl group having 1 to 10 carbons and 1 to 3 double bonds, alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or a trialkylsilyl or trialkylsilyloxy group where the alkyl groups independently have 1 to 6 carbons;

A is $(CH_2)_q$ where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is hydrogen, $COOH$, NO_2 , $P(O)(OH)_2$, $P(O)(OH)OR_8$, $P(O)(OR_8)_2$, SO_2OH , $SO_2(OR_8)$, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} , CHO , $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or tri-lower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons, or a pharmaceutically acceptable salt of said compound.

2. (Original) A method in accordance with Claim 1 where X is $(C(R_1)_2)_n$ and n is 1.
3. (Original) A method in accordance with Claim 1 where X is S.
4. (Original) A method in accordance with Claim 1 where X is O.
5. (Original) A method in accordance with Claim 1 where X is NR .
6. (Original) A method in accordance with Claim 1 where Y is phenyl.
7. (Original) A method in accordance with Claim 1 where Y is thienyl.

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8. (Original) A method in accordance with Claim 1 wherein said compound has a structure selected from formulas (1) and (2).

9. (Original) A method in accordance with Claim 8 wherein said compound has a structure of formula (1) where the dashed line represents absence of a bond.

10. (Original) A method in accordance with Claim 8 wherein said compound has a structure of formula (1) where the dashed line represents a bond.

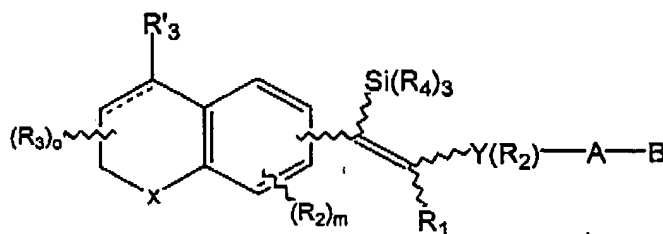
11. (Original) A method in accordance with Claim 1 wherein said compound has a structure selected from formulas (3) and (4).

12. (Original) A method in accordance with Claim 11 wherein said compound has a structure of formula (3) where the dashed line represents absence of a bond.

13. (Original) A method in accordance with Claim 11 wherein said compound has a structure of formula (3) where the dashed line represents a bond.

14-30 (Cancelled)

31. (Previously amended) A method of treating a hypercholesterolemic mammal comprising the steps: administering to a mammal in need thereof a pharmaceutically acceptable composition comprising an FXR antagonist having the following formula



formula (3)

wherein the dashed line represents a bond or absence of a bond;

X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons, or

X is $(C(R_1)_2)_n$ where R_1 is H or alkyl of 1 to 6 carbons, and n is an integer having the value of 0 or 1;

R₂ is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃, fluoro substituted

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alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 12 carbons, or alkylthio of 1 to 12 carbons, benzyloxy or $C_1 - C_{12}$ alkylbenzyloxy;

R_3 is hydrogen, lower alkyl of 1 to 6 carbons or F;

m is an integer having the value of 0 - 3;

o is an integer having the value of 0 - 4 when the dashed line represents absence of a bond, and 0 - 3 when the dashed line represents a bond;

R'_3 is hydrogen, lower alkyl of 1 to 6 carbons, F or $(R_{15})_r$ -phenyl, $(R_{15})_r$ -naphthyl, or $(R_{15})_r$ -heteroaryl where the heteroaryl group has 1 to 3 heteroatoms selected from the group consisting of O, S and N, r is an integer having the values of 0 - 5;

R_4 is alkyl of 1 to 8 carbons, or phenyl;

Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrolizolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups;

R_{15} is independently H, F, Cl, Br, I, NO_2 , $N(R_8)_2$, $NH(R_8)$, COR_8 , $NR_8CON(R_8)_2$, OH, $OCOR_8$, OR_8 , CN, an alkyl group having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10 carbons, an alkenyl group having 1 to 10 carbons and 1 to 3 double bonds, alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or a trialkylsilyl or trialkylsilyloxy group where the alkyl groups independently have 1 to 6 carbons;

A is $(CH_2)_q$ where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is hydrogen, COOH, NO_2 , $P(O)(OH)_2$, $P(O)(OH)OR_8$, $P(O)(OR_8)_2$, SO_2OH , $SO_2(OR_8)$, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} , CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or tri-lower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons, or a pharmaceutically acceptable salt of said compound.

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32. (Currently amended) A method of treating an FXR-mediated pathological condition in a mammal comprising the step of providing to said mammal a pharmaceutically acceptable composition comprising a synthetic FXR ligand able to stimulate, block, or inhibit the activity of a mammalian FXR receptor.

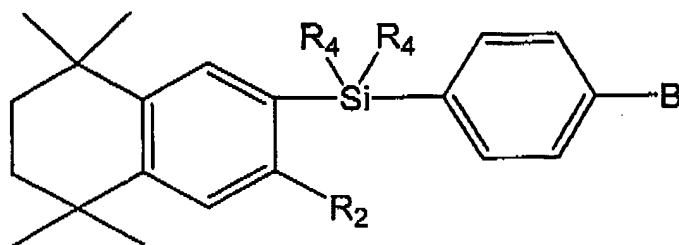
33. (Original) The method of claim 32 wherein said pathological condition comprises hypercholesterolemia.

34. (Original) The method of claim 32 wherein said pathological condition comprises hypocholesterolemia.

35. (Original) The method of claim 32 wherein said pathological condition is characterized by the overproduction of bile acids.

36. (Original) The method of claim 32 wherein said pathological condition is characterized by the underproduction of bile acids.

37. (Currently amended) A method of treating an FXR-mediated pathological condition in a mammal comprising the step of administering to a mammal in need thereof a pharmaceutically acceptable composition comprising a synthetic FXR ligand able to stimulate, block, or inhibit the activity of a mammalian FXR receptor, said synthetic FXR ligand having the formula



wherein R_2 is H or lower alkyl, R_4 is lower alkyl of 1 to 8 carbons and B is CH_2OH or $COOR_8$ where R_8 is H or ethyl.

38. (Original) A method in accordance with Claim 31 where R_2 is H and R_4 is ethyl.

39. (Original) A method in accordance with Claim 32 where B is CH_2OH .

40. (Original) A method in accordance with Claim 33 where B is $COOR_8$.